August 7, 2018

Personal Matters / Ex. 6

Email: Personal Email / Ex. 6

Mr. Andrew Wheeler
Acting Administrator
United States Environmental Protection Agency
Mail Stop 1101A
1200 Pennsylvania Ave. NW
Washington, DC 20460

Dear Acting Administrator Wheeler,

As a retired EPA toxicologist formerly associated with the Office of Pesticide Programs (OPP), I know first hand the frustrations of having to deal with epidemiological reports from the open literature.

I believe that Mr. Pruitt's directive regarding transparency in regulatory decisions especially related to epidemiological studies has merit. With this communication, I hope to provide a path forward that will produce a document that clearly indicates that the EPA conducted a thorough critical review of epidemiological studies occurring in the open literature or otherwise. The resulting document will clearly articulate the basis for its decision to allow the use of such publications to impact the risk assessment or determine that the study does not provide sufficient proof for its conclusions.

First of all, there is a great discrepancy in the review of the toxicology studies that industry is required to submit in order to register their chemical products. These studies follow strict protocol guidelines and are conducted under stringent good laboratory practices (GLP), quality assurance (QA) and animal ethics reviews as well as rigid reporting standards. These studies in the OPP have multiple layers of primary and secondary review most often by contractors at a very significant expenditure of taxpayer funds and program resources. The studies are essentially transcribed into Data Evaluation Records (DERs) that have to state what was done and what the results were since the reviewers cannot misrepresent what the study reported. The reviewers, however, can indicate study deficiencies and identify responses not already indicated by the report. The reviewers responsible for the reviews are clearly identified and responsible for their decisions.

In marked contrast, epidemiological studies appearing in the open literature (or otherwise) follow a mixed bag of study designs, GLP, QA, ethics and reporting practices. However, these studies are most often accepted at their face value without evidence of a critical review or identification of the responsible individuals.

This practice is unfair to the public. Studies used for risk assessment should have the same level of critical review no matter what their source is.

A current example is how the OPP handled chlorpyrifos that I have personal experience with. The most recent SAP review indicated problems with the original Columbia epidemiological study that should have been resolved long before several previous expensive SAP meetings were held. There are no similar DER reviews indicating the responsible reviewers provided to support the OPP's actions or attempts to use the study endpoints for risk assessment that I know of.

With the concept of a disparity in the degree of review of animal studies conducted to support the registration of a pesticide (or other chemical) and the acceptance of epidemiological studies on their face value, I am proposing that:

An Epidemiological Study Peer Review Council be established with the goal of creating a transparent document reflecting a thorough review of the study be established by EPA.

The details of this Council are in the attached document entitled "**Proposal for the Review of Epidemiology Studies from the Open Literature (or otherwise) Being Considered for a Basis for Regulatory Action: Establishment of Agency Wide Epidemiology Study Peer Review Council (ESPRC) and the resulting product Record of Epidemiology Study Review (ROESR).**"

The resulting product should provide a transparent assessment and whether or not an epidemiology study can be used for risk assessment. The responsible individuals are identified and would defend their decisions from objections from either industry or public interest groups.

I certainly hope that you will find this proposal helpful and forward it to the appropriate individuals concerned with evaluation of toxicity and risk assessment. If there are questions concerning how this Council could be implemented, please contact me. I will be happy to make a presentation on how this Council can contribute to the goal of making transparent decisions for risk assessment. Electronic copies of the proposal can be provided on request from EPA staff.

Thank you for giving this suggestion your consideration.

John D. Doherty, Ph.D.
(DABT 1982-2017)
Independent Toxicologist
Email: Personal Email / Ex. 6

PS. This proposal was presented at the afternoon session of the open meeting on Transparency held on July 17, 2018.

August 7, 2018

Subject: **Proposal for the Review of Epidemiology Studies from the Open Literature (or otherwise) Being Considered for a Basis for Regulatory Action: Establishment of Agency Wide Epidemiology Study Peer Review Council (ESPRC) and the resulting product Record of Epidemiology Study Review (ROESR).**

To: **Mr. Andrew Wheeler**
Acting Administrator
Environmental Protection Agency
Mail Code 1101A
1200 Pennsylvania Ave NW
Washington, DC 20460

From: **John D. Doherty, Ph.D.**
(DABT: 1982-2017)
Email: Personal Email / Ex. 6

As a retired toxicologist in the EPA's Office of Pesticide Programs, I believe that there is merit to Mr. Pruitt's directive that only studies where the public can review the supporting data can be used for regulatory decisions. Epidemiological studies should not be accepted based on their face value without critical evaluation of all aspects of the study. I also recognize that such supporting data may not be available because of various reasons including the confidentiality of the subjects in the study cohort.

There should be a middle ground where the Agency determines that the study can be used for regulatory decisions when all supporting data are not available. The decision to use the study in the absence of an independent review of the original data should *not be* the responsibility of one individual. The following is a proposal to justify the use of an epidemiological study when not all of the supporting data are available. Or to otherwise state clearly why the study cannot be used without the submission of additional data.

A Call for the Standardization of the Review of an Epidemiology Studies – Establishment of an Agency wide Epidemiology Study Peer Review Council (ESPRC) and the product Record of Epidemiological Study Review (ROESR).

Each epidemiology study occurring in the open literature or otherwise needs to have a supporting formal **Record of Epidemiological Study Review (ROESR)** that clearly delineates the justification for a decision to include or not include the study in the regulatory decisions for the chemical or environmental situation. The production of the ROESR will consist of the separate and independent reports of several Sub-Committees that will be integrated by the **Epidemiological Study Peer Review Council (ESPRC)** and signed by the Council Chairperson and each Council member.

It is important to have *independent* Sub-discipline committees review the study so that the biases of other sub-disciplines are minimized. The Sub-committee members should be drawn from the relevant staff throughout the Agency as well as other government agencies as needed. Each member of the Sub-committees will sign their respective Sub-committee reports.

The roles of the six suggested Sub-Committees and Council Chairperson are as follows:

1. ***Ethics Evaluation Sub-Committee.*** This sub-committee will evaluate all aspects of the ethical treatment of the individuals in the cohorts. This includes that it will identify how additional data can be provided to the Agency in a manner that will assure the identities of the individuals are protected.

2. ***Endpoint Evaluation Sub-Committee:*** This evaluation would limit its conclusions with regard to how well the character of the endpoint itself was assessed for and whether or not the effect reported is plausibly related to treatment or within normal variation. The latter includes how many subjects in a cohort are needed to make a meaningful statistical difference for the particular lesion in question.

This Sub-committee will provide commentary on the consistency of characterization of the endpoint, resolution of confounds as well as any known other chemicals or conditions that affect the normal distribution of the endpoint.

The experts in this Sub-committee will vary depending upon the endpoint claimed by the epidemiological study and consist of experts in cancer, behavioral response, or other appropriate discipline for interpretation of the significance of the endpoint.

3. Exposure Assessment Sub-Committee: The role of the exposure assessment Sub-committee is limited to determining that the methodology and reliability used to determine the exposure of the cohort is adequate and appropriate. The Sub-committee would provide commentary on whether or not exposure was supported by analytical chemical data, by oral history or otherwise. Also, if the actual persons exposed provided oral history by direct conversation, survey or by telephone. The committee will determine if indirect exposure information was provided by a relative (or friend or coworker) is reliable.

4. ***Statistical Evaluation Sub-Committee***: In the initial review of the study, the sole role of the statistical evaluation sub-committee is limited to determining if the statistical methods were/were not appropriate and adequately conducted to support the conclusion of the report. This committee would not redo the statistics at this time since the original data would be needed. Input from Sub-committees 1 (ethics), 2 (3ndpoint evaluation) and 3 (exposure assessment) that clarifies all

issues that are the responsibility of their respective disciplines would be needed before statistical reanalysis could be conducted. Thus, receipt of the original data in a manner that satisfies Sub-committees 1, 2 and 3 and well as any requests by the Statistical Evaluation Sub-committee before any statistical reanalysis would be conducted.

5. Analytical Chemistry Assessment Sub-Committee: The role of the analytical chemistry committee is limited to determining if the analytical techniques/ methodology were appropriate and adequate for the study. In some cases where no analytical chemistry data were generated, the committee will comment on the need to have included such data and/or if quantitative analysis of exposure data was even possible.

6. Animal Toxicity and Structure Activity Relationship (SAR) Assessment Sub-Committee: In most cases with chemicals, the Agency should already have a battery of standard animal toxicity studies that were required for the registration of that chemical. There may also be studies in the open literature attempting to define the toxicity of the chemical. Thus, the person(s) responsible for evaluating the animal toxicity studies would be a member of this Sub-committee. In addition, this Sub-committee will have individuals that can address the SAR issues in relation to the possibility that the chemical could affect the endpoint in question.

It should be noted here that a Record of Review (ROR) signed by at least two qualified toxicologist is needed for any publication supporting a mechanism of action for the chemical.

If the endpoint occurs in animals or has SAR correlates, such information can support the epidemiological findings. If not, it does not automatically dismiss the epidemiological findings since the effect on the endpoint may be unique to humans.

7. Council Chairperson, Council meetings and resulting product: ROESR:

The ***Council Chairperson*** should not be in the same program that has responsibility for regulating the chemical or environmental condition. That is, if the chemical is a pesticide, the Chairperson cannot be from the Office of Pesticide Programs (OPP). Representatives of OPP may still be on the Council if an epidemiological study with a pesticide is being reviewed.

At the initial **Council meeting,** the Council will discuss the conclusions of each the six Sub-committees. In some cases, the Council may determine that the association between exposure and the endpoint is otherwise strong enough to support regulatory action to protect the public health and no additional information is needed from the study authors.

During the initial meeting the Council can overrule a request for additional data made by any of the Sub-Committees. However, clear justification for overruling a Sub-Committee's decisions must be provided.

In other cases, the Council may determine that there is a definite need to require additional data supporting the study methodologies and conclusions are required. The Council would then notify the authors articulating of the need for the specific additional information.

The Council will also determine if the authors of the epidemiological report should be requested to attend a closed meeting with the Council and Sub-committee members. The purpose of the meeting will be an opportunity for the study authors to address any concerns that the Sub-committees have. This will include problems with providing any additional information that the Sub-committees requested. If the study authors refuse to attend a requested meeting, the Council will determine if the study should be rejected outright.

The Council Chairperson (or secretary of the Council) will prepare the **ROESR** product that contains the decision with supporting justification. The ROESR product would include the report of the Council with the Chairperson and Council members' signatures. Separate attachments for the *signed* Sub-Committee reports and the original epidemiological report (i.e. a publication) will also be attached. An executive summary of any meeting(s) with the study authors will also be appended.

Purpose:

The purpose of this procedure is to assure that responsible persons for each of the critical Sub-disciplines *independently* reviewed the study in terms of their expertise. The resulting ROESR that either determines that the study can be used in the absence of additional original data or the need for critical additional data is determined will be clearly indicated.

The Council Chairperson and members of the Council and the sub-discipline committees own their decisions and are responsible for defending them.

If industry or any concerned public interest groups object to the conclusions, they can address the conclusions presented in the ROESR and/or the sub-disciplines.

Therefore the decisions in the resulting ROESR should be transparent. The current system renders too much power to individuals that are sometimes not clearly identified who can profit by making career projects for themselves based on the face value of the publication.

I am well aware that an epidemiological publication (or otherwise) in the open literature is going to be controversial. However, preparing a ROESR for such studies with the several sub-disciplines all independently contributing to the Agency's determination of the conclusions in the report should greatly help to minimize controversies.

The ROESR is not a final conclusion (no documents in EPA should be considered final). It is very likely that a Science Advisory Panel will ultimately review the ROESR. Also, as new information is generated, the ROESR can be updated and the recommendations for use (or otherwise) can be adjusted as appropriate.

John Doherty PhD

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AUG 1 0 2018

Andrew Wheeler

RETURN RECEIPT REQUESTED

[Act]ing Administrator

[Uni]ted States Environmental Protection Agency

[M]ail Stop 1101A

[1]200 Pennsylvania Ave. N.W.

Washington, DC 20460

Route **EPA Mail**

[To]: Wheeler, Andrew

[M]ailstop ARN

[D]epartment: 1101A

[C]ertified

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